MANAGEMENT OF INTRACRANIAL ARTERIOSTENOSIS

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Objectives

At the completion of this presentation, participants will be able to discuss:

• Natural history of intracranial vascular disease

• Medical management of intracranial arteriostenosis

• Endovascular management of intracranial arteriostenosis

NATURAL HISTORY OF INTRACRANIAL ARTERIOSTENOSIS
Atherosclerotic intracranial stenosis

- May be most important cause of stroke in the world
- Incidence differs by race and ethnicity
  - White persons: 5-10% of strokes
  - Black persons: 15-30% of strokes
  - Asian persons: 30-50% of strokes
- Risk of stroke varies by
  - Symptomatic vs non-symptomatic lesions
  - Vessel location: highest risk in stenotic basilar artery
- Atherosclerotic intracranial arterial stenosis is associated with a high risk of recurrence, at least 12% in the first year

Atherosclerotic intracranial stenosis

Most commonly involved arteries (from WASID) --
- ICA 21%
- MCA 32%
- Vertebral artery 19%
- Basilar artery 20%
- Multiple vessels 6%

Mechanisms of ischemia in ICAD

- Hypoperfusion
  - Borderzone infarcts
- Artery to artery embolism and in situ thromboembolism
  - Territorial infarcts
- Perforator orifice occlusion
  - Deep subcortical
- Mixture of mechanisms
Stroke risk factors (WASID)

Recurrent stroke risk in persons with symptomatic ICAS is associated with:

- Higher for stenosis ≥ 70%
- Higher risk in blacks
- Higher in women (28%) than men (17%) at 2 years
- Poorer collaterals

Risk Factors associated with ischemic stroke (WASID)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Event Rate + Risk Factor</th>
<th>Event Rate − Risk Factor</th>
<th>Hazard Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &gt; 140 mm Hg</td>
<td>23%</td>
<td>15%</td>
<td>1.6</td>
<td>P=0.012</td>
</tr>
<tr>
<td>MAP &gt; 107 mmHg</td>
<td>38%</td>
<td>15%</td>
<td>2.8</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Hgb A1c &gt; 7</td>
<td>26%</td>
<td>15%</td>
<td>1.7</td>
<td>P=0.15</td>
</tr>
<tr>
<td>Any Smoking</td>
<td>20%</td>
<td>18%</td>
<td>1.1</td>
<td>P=0.63</td>
</tr>
<tr>
<td>No Alcohol</td>
<td>23%</td>
<td>15%</td>
<td>1.8</td>
<td>P=0.003</td>
</tr>
</tbody>
</table>

Risk Factors associated with ischemic stroke (WASID)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Event Rate + Risk Factor</th>
<th>Event Rate − Risk Factor</th>
<th>Hazard Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol ≥ 200</td>
<td>23%</td>
<td>12%</td>
<td>2.1</td>
<td>P=.0006</td>
</tr>
<tr>
<td>LDL ≥ 100</td>
<td>19%</td>
<td>12%</td>
<td>1.7</td>
<td>P=0.033</td>
</tr>
<tr>
<td>LDL ≥ 70</td>
<td>17%</td>
<td>7%</td>
<td>2.2</td>
<td>P=0.23</td>
</tr>
<tr>
<td>HDL &lt; 40</td>
<td>19%</td>
<td>15%</td>
<td>1.3</td>
<td>P=0.23</td>
</tr>
<tr>
<td>Triglycerides ≥ 200</td>
<td>20%</td>
<td>15%</td>
<td>1.4</td>
<td>P=0.15</td>
</tr>
</tbody>
</table>
Risk Factors of Intracranial Arteriosclerosis

**Major Risk Factors**
- Hypertension
- SBP >140 mm Hg
- Hyperlipidemia
  - Mean cholesterol >200 mg/dl
- Smoking
- Diabetes mellitus

**Other Risk Factors**
- Metabolic syndrome
- Reduced adiponectin
- Increased CRP, PAI-1, lipoprotein(a), E-selectin, phospholipase A2

Effects of Extracranial Carotid Stenosis on Intracranial Blood Flow

- Study of 44 carotid stenosis patients who had undergone both vessel flow rate measurements (w. quantitative MRA) and digital subtraction angiography
- Percentage stenosis and residual lumen are significantly associated with ICA flow
- MCA flow ratio was not significantly associated with percentage stenosis, stenosis length, or residual lumen
- This suggests that local hemodynamic effects of carotid stenosis do not translate directly to distal vasculature, because intracranial flows can be maintained through collaterals.


DIAGNOSTIC EVALUATIONS OF INTRACRANIAL ARTERIOSTENOSIS
Diagnostic Imaging

- TCD and MRA have high negative predictive values (86-91%) but low positive predictive values (36-59%) based on data from SONIA substudy of WASID
- CTA is better than MRA at detecting >50% stenosis
- Conventional cerebral angiography remains gold standard for detecting degree of intracranial luminal stenosis
- Quantitative MRA (TOF and phase contrast) to derive volumetric flow rates in specific vessels
- Fractional flow reserve: index to derive pressure gradient across a stenosis

Diagnosis: Magnetic Resonance Angiography in MCA

The flow gap suggests a flow-limiting stenosis

Diagnosis: Catheter Angiography of MCA

Risk of recurrent stroke is 23% in 1 year
MEDICAL MANAGEMENT OF INTRACRANIAL ARTERIOSTENOSIS

Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis

- Randomized, double-blind multicenter trial of warfarin (target INR 2-3) vs Aspirin (1300 mg daily) in persons (≥40 yo) with TIA or non-disabling stroke in territory of ICAS, angiographically proven to be >50%
- Primary endpoint: ischemic stroke, brain hemorrhage or death from vascular cause other than stroke during follow-up
- 567 persons enrolled between 1999 and 2003. Stopped early due to safety concerns of those on warfarin

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin (N=208)</th>
<th>Warfarin (N=209)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ischemic stroke, brain hemorrhage, or death from vascular cause</td>
<td>32 (15.3)</td>
<td>8 (3.9)</td>
<td>1.8 (1.05-3.16)</td>
<td>0.03</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke or transient ischemic attack</td>
<td>56 (26.7)</td>
<td>49 (23.1)</td>
<td>1.03 (0.63-1.68)</td>
<td>0.91</td>
</tr>
<tr>
<td>Ischemic stroke in territory of symptomatic stenosis</td>
<td>47 (22.8)</td>
<td>13 (6.2)</td>
<td>2.16 (0.85-5.51)</td>
<td>0.11</td>
</tr>
<tr>
<td>Death from nonatherosclerotic causes</td>
<td>25 (12.1)</td>
<td>13 (6.2)</td>
<td>1.64 (0.62-4.48)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

WASID: primary and secondary endpoints
WASID

- Study of location, type (lacunar vs. non-lacunar), cause, and severity of stroke WASID participants who had ischemic endpoint (n=106) during 1.8 year follow-up.

  - Nearly half of the strokes in the territory are disabling.
  - Most common cause of stroke out of the territory was a previously asymptomatic intracranial stenosis.
  - Penetrating artery disease was responsible for a low number of strokes.


Lacunar Stroke in WASID

- WASID: 347 enrolled after an index stroke
  - 38 lacunar and 309 nonlacunar

- Stroke recurrence (mean follow-up of 1.8 years)
  - no significant difference in stroke recurrence between patients w. index lacunar stroke (18%) vs nonlacunar (22%)
  - no significant differences were found when groups were stratified by 50% to 69% stenosis and >70% stenosis.
  - Of the 7 recurrent strokes in patients whose index stroke was lacunar, all 7 were nonlacunar, w. 3 in territory of stenotic artery.

  Conclusions—Findings suggest that these strokes are due to stenosis (or occlusion of ostium) in parent vessel (or due to artery-to-artery embolism from the parent to the penetrating artery) rather than small vessel disease.

Infarct patterns, collaterals and likely causative mechanisms of stroke in symptomatic intracranial atherosclerosis.

WASID study participants
- Baseline infarcts (n=136)
  - Artery-to-artery embolic mechanism in 50.7%
  - Perforator occlusion in 25%,
    - More common in posterior circulation
  - Hypoperfusion in 9%
  - Mixed in 15.5%,
    - Combined small pial or scattered multiple cortical infarcts with infarcts in border-zone regions
    - More common in anterior circulation
- Recurrent infarcts (n=47)
  - Artery-to-artery embolic mechanism in 61.7%


Medical Management of Intracranial Arteriostenosis
- Dual antiplatelet treatment
  - Aspirin 325 mg + Clopidogrel 75 mg X 3 mos, then aspirin 325 mg daily
  - Cilostazol 100 mg bid + Aspirin (75 mg-150 mg) daily is alternative
- Intensive management of risk factors
  - Especially SBP and Lipids

PROCEDURAL MANAGEMENT OF INTRACRANIAL ARTERIOSTENOSIS
Surgical treatment
1985: EC/IC Bypass study 1377 participants with extracranial carotid occlusion or intracranial ICA or MCA stenosis randomized to either:
- Superficial Temporal Artery to Middle Cerebral Artery (M2 branch) bypass
- Medical therapy with aspirin (325 mg 4 times daily) and BP management
- Procedure did not lower risk of stroke more that those taking aspirin
2011: Carotid Occlusion Surgery Study (COSS) evaluated patients with ipsilateral ischemic events related to intracranial artery occlusion.
Patients were randomized if they had increased oxygen extraction fraction.
- Medical treatment vs EC/IC bypass surgery.
- Procedure did not lower risk of stroke more than taking aspirin (21% vs 23%).

SAMMPRIS
Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis
- Objective: To determine whether intracranial stenting and intensive medical therapy is superior to intensive medical therapy alone for preventing stroke in recently symptomatic patients with severe intracranial atherosclerotic stenosis.
- Design: Phase III, multi-center, randomized, open label trial
- Setting: 50 sites in the US
- Subjects: Patients w. recent TIA or stroke attributed to stenosis of 70 to 99% of the of a major intracranial artery.
- Intervention: Eligible patients were randomized to receive either aggressive medical medical management alone or aggressive medical management plus PTAS with the use of the Wingspan stent system.

Wingspan Stent System
The Gateway angioplasty balloon and Wingspan stent (only FDA approved device at the time of the study) were the only devices allowed in the SAMMPRIS trial.
SAMMPRIS

TIA or Stroke attributed to 70-99% of major intracranial artery:

- Aggressive medical management versus
  Aggressive medical management + PTAS with Wingspan stent

- Aggressive medical management:
  - Aspirin 325 mg daily (throughout study) + Clopidogrel 75 mg daily (x 90 days)
  - Management of SBP (<140 mmHg), LDL<70 with anti-hypertensives, statin (rosuvastatin)
  - Lifestyle program: DM, non-HDL, smoking, weight, exercise

SAMMPRIS Methods

Primary endpoint: Stroke or death within 30 days of enrollment or revascularization during follow-up OR stroke in the territory of the stenotic/stented artery beyond 30 days

- Enrollment was stopped after 451 patients underwent randomization because of the high risk of peri-procedural stroke or death in the PTAS group (14.7%) and a low risk of stroke in the medical treatment group (5.8%).

- Final results: During a median follow-up of 32.4 months, the primary endpoint was significantly higher in those receiving PTAS (23%) compared with those receiving aggressive medical therapy alone (15%).

SAMMPRIS: Comparison of Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Medical group (n=227)</th>
<th>PTAS group (n=224)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Patients w. Event</td>
<td>% Patient w. Event</td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>15%</td>
<td>23%</td>
<td>0.025</td>
</tr>
<tr>
<td>Any stroke or death</td>
<td>23%</td>
<td>29%</td>
<td>0.13</td>
</tr>
<tr>
<td>Any death</td>
<td>6%</td>
<td>6%</td>
<td>0.90</td>
</tr>
<tr>
<td>Any stroke</td>
<td>19%</td>
<td>26%</td>
<td>0.047</td>
</tr>
<tr>
<td>Disabling or fatal stroke</td>
<td>8%</td>
<td>9%</td>
<td>0.51</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4%</td>
<td>2%</td>
<td>0.34</td>
</tr>
<tr>
<td>Major non-stroke hemorrhages</td>
<td>4%</td>
<td>4.4%</td>
<td>0.11</td>
</tr>
<tr>
<td>Any major hemorrhages</td>
<td>4%</td>
<td>13%</td>
<td>0.0009</td>
</tr>
</tbody>
</table>
Strokes in SAMMPRIS

- Of the 224 patients randomized to the WS arm who underwent stenting (n=219) or angioplasty alone (n=5)
  - 13 had hemorrhagic stroke
    - 4 of the 13 were SAH
    - 7 of the 13 were intraparenchymal bleeds remote from stented vessel and association with
      - Higher degrees of intracranial stenosis
      - Administration of a preoperative clopidogrel loading w. 600mg
      - High procedural activated clotting time of >300 seconds

SAMMPRIS Conclusions

Aggressive medical management was superior to PTAS with Wingspan stent system because

- Risk of early stroke after PTAS was high
- Risk of stroke with aggressive medical therapy alone was lower than expected
Intracranial stenosis: impact of randomized trials on treatment preferences of US neurologists and neurointerventionists

<table>
<thead>
<tr>
<th></th>
<th>Pre-WASID</th>
<th>Post-WASID</th>
<th>Post-SAMMPRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet as treatment of ICAS in Anterior Circ.</td>
<td>44%</td>
<td>85%</td>
<td>94% Aspirin + Clopidogrel</td>
</tr>
<tr>
<td>Antiplatelet as treatment of ICAS in Posterior Circ.</td>
<td>36%</td>
<td>74%</td>
<td>83% Aspirin + Clopidogrel</td>
</tr>
<tr>
<td>Neurologists recommending PTAS in &gt;25% of pts with ICAS</td>
<td>0%</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Neurointerventionists recommending PTAS in &gt;25% of pts with ICAS</td>
<td>49%</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>


Incidence and Risk Factors for Diffusion-Weighted Imaging (+) Lesions After Intracranial Stenting and Its Relationship With Symptomatic Ischemic Complications

Park KY et al. Stroke 2014;45:00-00

Methods:
- A total of 123 patients (male:female=88:35, mean 64 yr) with symptomatic ICAS (mean stenosis 76.1±7.7%) who underwent both stenting and post-stenting DWI.

Risk Factors for Diffusion-Weighted Imaging (+) Lesions After Intracranial Stenting

<table>
<thead>
<tr>
<th>Embolic infarction alone</th>
<th>Mixed type of stenosis-associated perforator infarct and embolic lesions</th>
</tr>
</thead>
</table>

Stroke. 2014;45:00-00
Incidence and Risk Factors for Diffusion-Weighted Imaging (+) Lesions After Intracranial Stenting and Its Relationship With Symptomatic Ischemic Complications

- The incidence of DWI (+) after intracranial stenting for intracranial atherosclerotic stenosis was 35.0%.
- Middle cerebral artery, smaller distal parent artery, and treatment-related dissection were independent risk factors for DWI (+).
- Symptomatic ischemic complications occurred more frequently in the stenosis-associated perforator/mixed type (3/11, 27.3%) than in the embolic-alone type (1/32, 3.1%; \( P < 0.05 \)).

Safety of Low-Dose Aspirin in Endovascular Treatment for Intracranial Atherosclerotic Stenosis

- **Objectives**: To evaluate the safety of low-dose aspirin plus clopidogrel versus high-dose aspirin plus clopidogrel in prevention of vascular risk within 90 days of duration of dual antiplatelet therapy in patients treated with intracranial endovascular treatment.
- **Methods**: 370 patients with symptomatic 70% ICAS undergoing endovascular treatment. Antiplatelet therapy consists of aspirin, at a low-dose of 100 mg or high-dose of 300 mg daily; clopidogrel, at a dose of 75 mg daily for 5 days before endovascular treatment. The dual antiplatelet therapy continued for 90 days after intervention.
- **Endpoints**: acute thrombosis, subacute thrombosis, stroke or death within 90 days after intervention.

- **Results**: 273 patients received 100 mg aspirin plus 75 mg clopidogrel and 97 patients received 300 mg aspirin plus 75 mg clopidogrel before intracranial endovascular treatment.
- **Within 90 days after intervention for low dose vs high dose**:
  - Acute thrombosis: 1.5% vs 0%
  - Subacute thrombosis: 1.8% vs 2.1%
  - Stroke: 6.2% vs 6.2%
  - Death: 0.7% vs 2.1%
- There were no differences in all study endpoints between the two groups.
- **Conclusion**: Low-dose aspirin plus clopidogrel is comparative in safety with high-dose aspirin plus clopidogrel within 90 days of duration of dual antiplatelet therapy in patients treated with intracranial endovascular treatment.
SUMMARY AND FUTURE DIRECTIONS

Treatment recommendations for symptomatic 50-99% ICAS

Based on results of WASID and SAMMPRIS

www.thelancet.com/neurology Vol 12 November 2013

Summary
- Conservative medical management is the appropriate first step in the treatment of ICAD.
- An endovascular treatment approach based on the mechanism of stroke may be beneficial for select patients.
- Patient selection will be a critical factor in the design of future ICAD clinical trials.
- Those in whom endovascular procedure may be indicated:
  1) Hemodynamic symptoms
  2) Poor collaterals
  3) Large imaging mismatch, with collateral failure
  4. Recurrent symptoms despite best medical tx
Potential Future Directions

• Newer safer stents
• Balloon Angioplasty without stenting
  • Risks: elastic recoil, dissection, emboli, rupture
  • Complications decreased (from 50% to 5%) with smaller, slower inflating balloons
• Indirect revascularization: Encephaloduroarteriosynangiosis
  • Donor arteries (STA or MMA) placed next to superficial brain arteries distal of stenosis so that a network of collateral can form
• Ischemic preconditioning: brief cycles of occlusion of both brachial arteries with BP cuff twice daily x 300 days decreased stroke rate (8% vs 27%, P<0.01)
• Direct thrombin and Xa inhibitors

Considerations for future trials

• >70% stenosis
• Exclude persons with Mori C lesions
• Angioplasty arm. Angioplasty with small, shorter balloons
• Stents should be used only as a bail out for large dissection or significant recoiling of the lesion following angioplasty
• Stratify based on MRA perfusion


THE END